6-30-1955

Intermediates for p-acetamidocinnamic ester synthesis

William Grayson Fix
New Jersey Institute of Technology

Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

INTERMEDIATES FOR p-ACETAMIDOCINNAMIC ESTER SYNTHESIS

BY

WILLIAM G. FIX

A THESIS
SUBMITTED TO THE FACULTY OF
THE DEPARTMENT OF CHEMICAL ENGINEERING
OF
NEWARK COLLEGE OF ENGINEERING

IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

OF

MASTER OF SCIENCE
IN CHEMICAL ENGINEERING

NEWARK, NEW JERSEY

1955

ABSTRACT

Intermediates for p-Acetamidocinnamic Acid Synthesis.

After a review of the various methods found in the literature, a series of reactions were selected which were reported to have good yields.

Using p-nitrotoluene as a starting material, a simultaneous oxidation and reduction with sodium polysulfide was investigated as a means of making p-aminobenzaldehyde. Experimental procedures and yields were reported, and improved methods of recovery were described.

Using p-aminobenzaldehyde from the first reaction, a condensation with malonic acid, in pyridine-piperidine medium, was investigated as a means of preparing p-aminocinnamic acid.

A recommended procedure was described, and some suggestions were made concerning the completion of the synthesis of p-acetamidocinnamic esters.

APPROVAL OF THESIS

FOR

DEPARTMENT OF CHEMICAL ENGINEERING

NEWARK COLLEGE OF ENGINEERING

BY

FACULTY COMMITTEE

APPROVED: _____

_____

_____

NEWARK, NEW JERSEY

JUNE, 1955

PREFACE

The purpose of this investigation has been an attempt to find a suitable series of intermediate steps which lead to the synthesis of p-acetamidocinnamic esters.

The development of these intermediate steps has particularly been directed toward attainment of maximum yields, and elimination of inefficient or difficult operations. In the preliminary review of methods from the literature, all those with low reported yields were automatically eliminated.

It is hoped that this work may have paved the way toward a commercially practical synthesis of these interesting compounds.

William G. Fix

Newark, N. J.
June, 1955.

ACKNOWLEDGMENT

To Professor Saul I. Kreps, who suggested the project, I would like to express my gratitude for the invaluable guidance and constructive criticism which he freely gave to me throughout my experimental work.

William G. Fix

TABLE OF CONTENTS

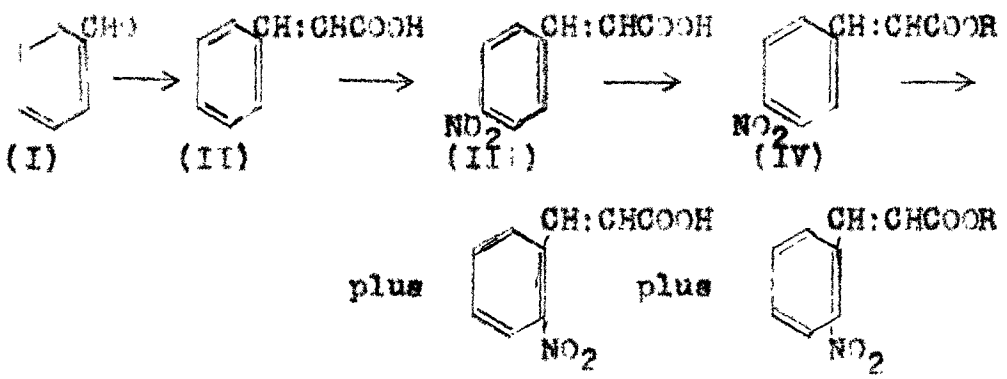
CONCLUSIONS AND RECOMMENDATIONS

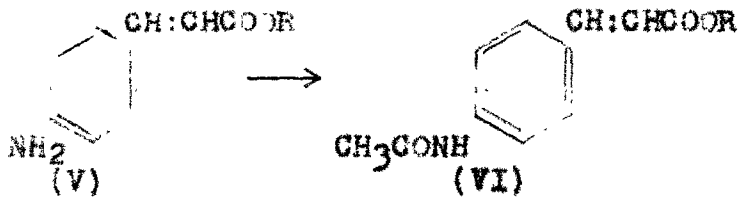
INTRODUCTION

Methods Available from the Literature

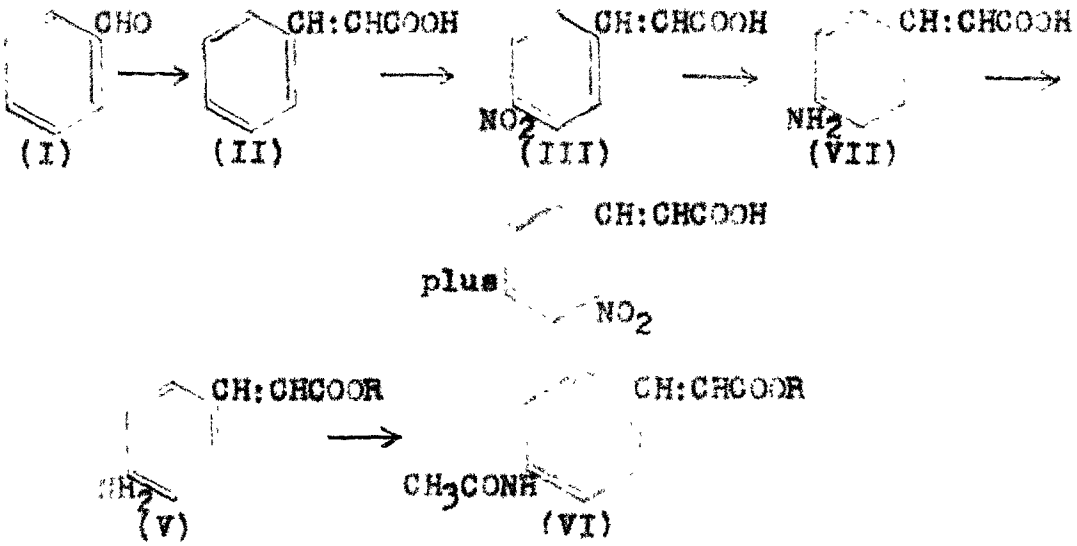
A preliminary search has revealed a number of possible intermediate routes through which the esters of p-acetamido-cinnamic acid may be synthesized. Although toluene is the basic starting material for most of the intermediates to be cited, it is a matter of convenience, in the synthesis of a fine chemical such as this, to start with one of the commercially available toluene derivatives. A few of these routes are outlined below:

Ia. Benzaldehyde (I); via Perkin's condensation[5,7,9,12,13,22,25] to cinnamic acid (II); via nitration[8,11,24] to O- and p-nitrocinnamic acids (III); via esterification, followed by separation of the p- isomer (IV);[8, 11] via reduction[6] to the p-amino-- ester (V); and acetylation to the p-acetamidocinnamic ester (VI).

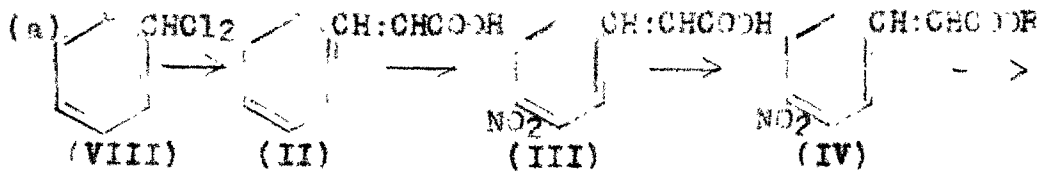


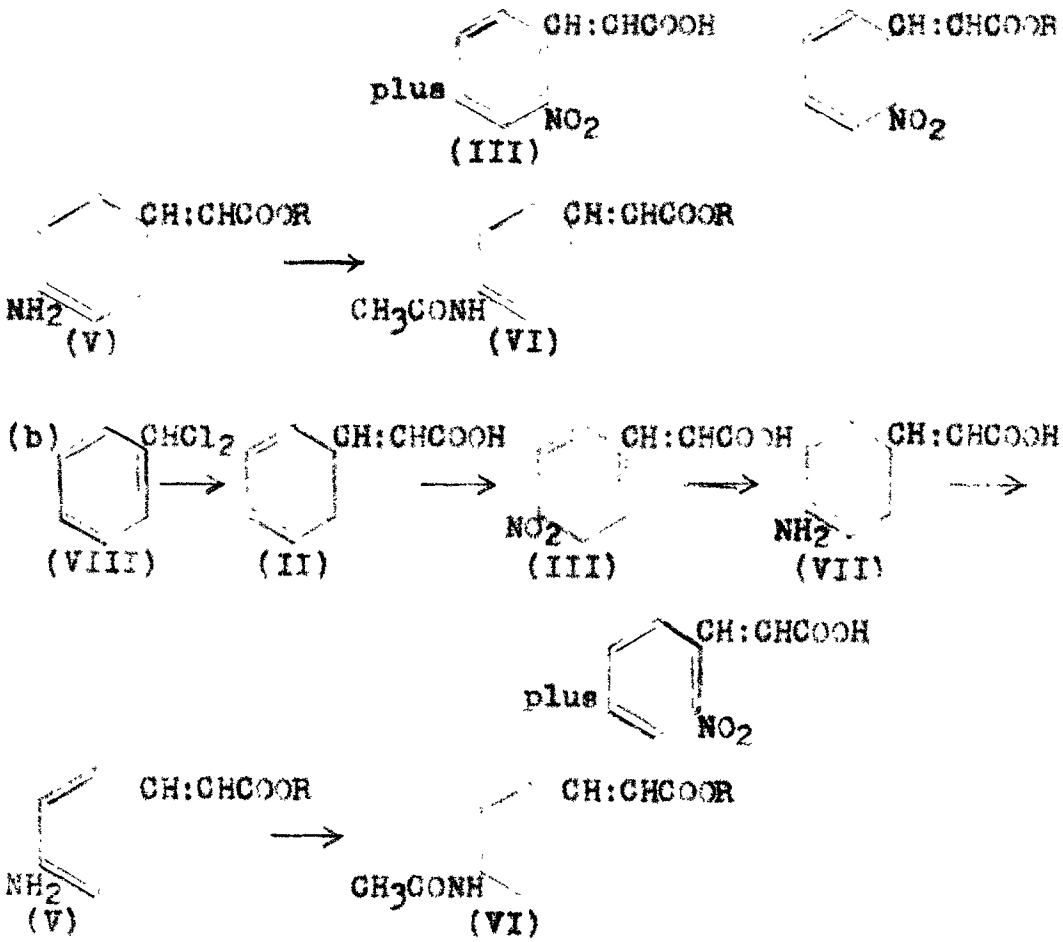


Ib. Benzaldehyde (I); treated as in Ia, except that p-nitrocinnamic acid (III) is isolated, and reduced[4] to p-aminocinnamic acid (VII); via esterification by the Fischer-Speier method; via acetylation to the p-acetamido cinnamic ester (VI).

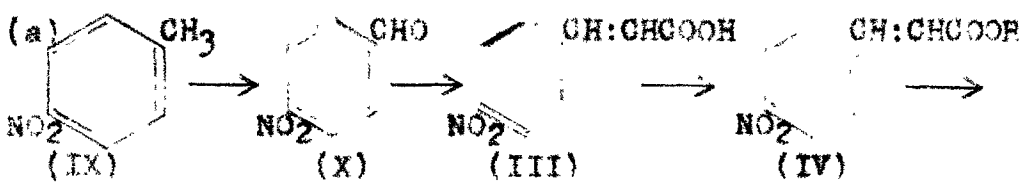


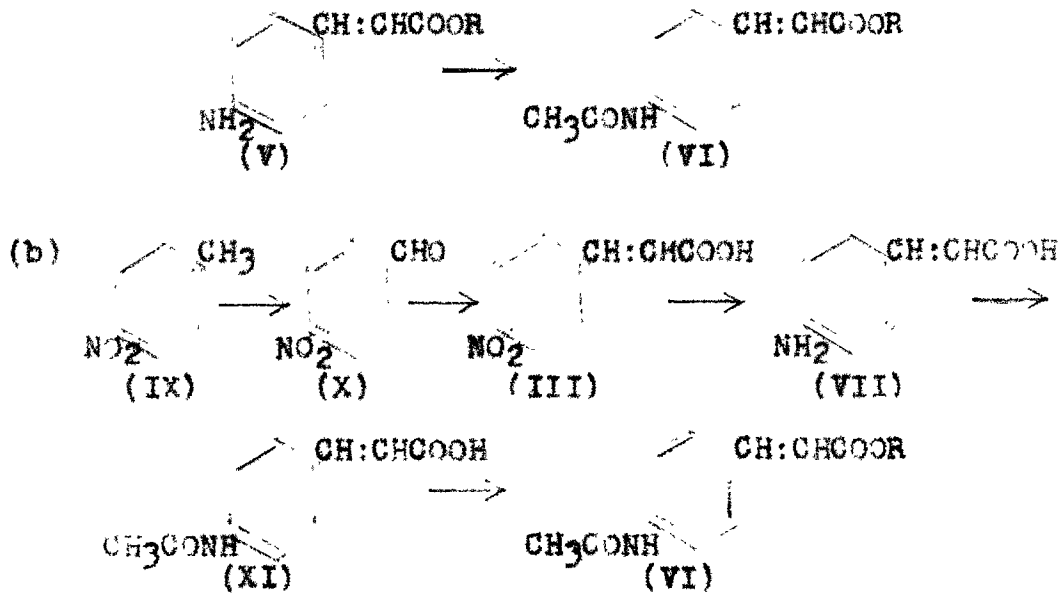
IIa. and IIb. Benzal chloride (VIII); via Caro's Method[3] to cinnamic acid (II); thence in the same manner as in Ia and Ib above.



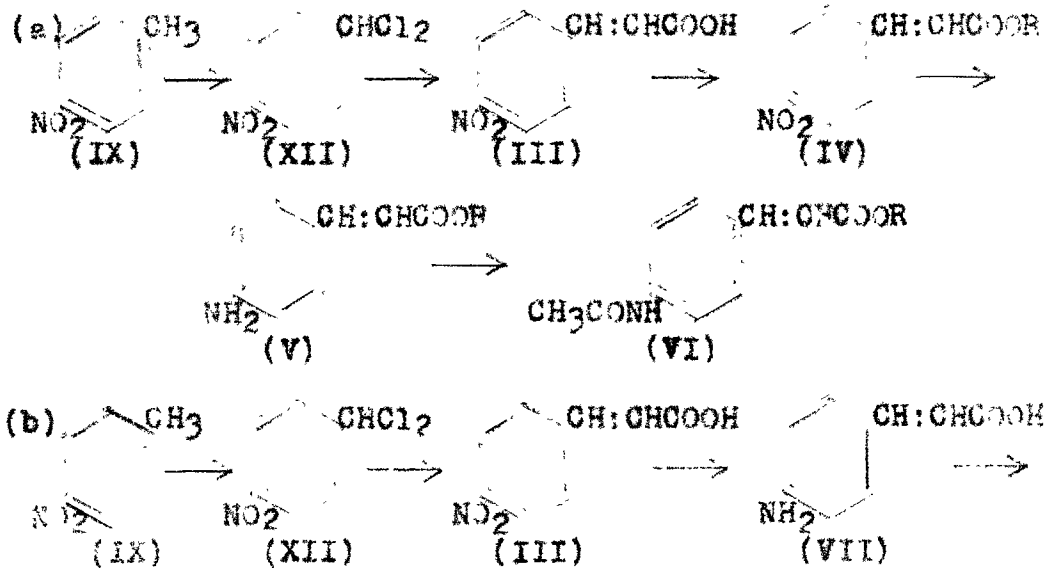


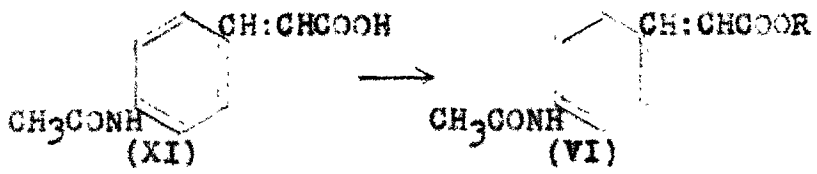
IIIa. and IIIb. p-Nitrotoluene (IX); via oxidation,[15,16] to p-nitrobenzaldehyde (X); via Perkins condensation[2,18] to p-nitrocinnamic acid (III); thence via acetylation either before (b) or after (a) esterification.



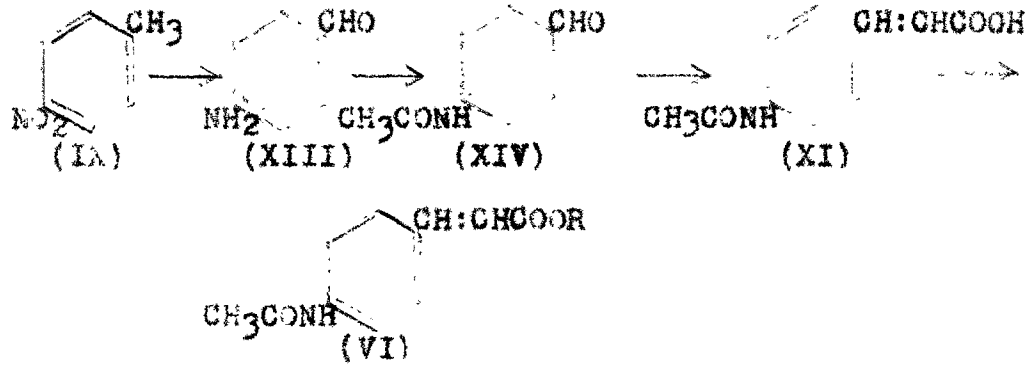


<u>IIIc. and IIId.</u> p-Nitrotoluene (IX); via chlorination to p-nitrobenzal chloride (XII); via Caro's method[3] to p-nitrocinnamic acid (III); thence as in IIIa and b.

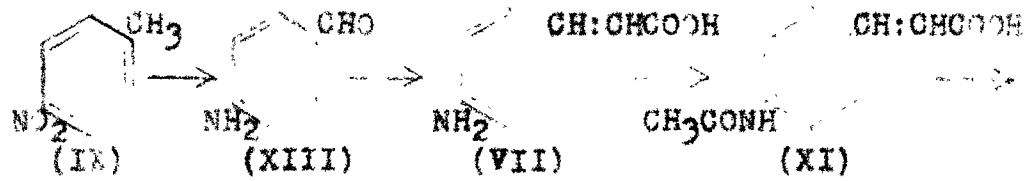


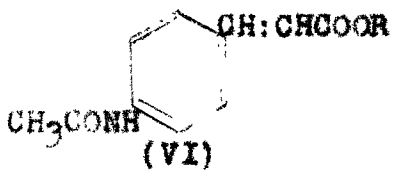


IIIe. p-Nitrotoluene (IX); via simultaneous oxidation and reduction[1,10,17,21,23,26,27] to p-aminobenzaldehyde (XIII); acetylation to p-acetamidobenzaldehyde (XIV); condensation with malonic acid[18,19,3] to p-acetamidocinnamic acid (XI); via esterification to p-acetamidocinnamic ester (VI).



IIIf. p-Nitrotoluene (IX); via oxidation and reduction as in IIIe; via condensation with malonic acid to form p-aminocinnamic acid (VII); via acetylation and subsequent esterification to p-acetamidocinnamic ester.





(VI)

Preliminary Considerations

The foregoing possibilities are narrowed down somewhat by a closer inspection of the methods used. In route Ia, the production of an expensive and useless by product, o-nitrocinnamic ester, is not economical. In route Ib, the separation of o- from p-nitrocinnamic acid, before esterification, may be difficult or nearly impossible.

In routes IIa and IIb, the same problems are encountered subsequent to the nitration of the cinnamic acid.

The routes under IIIa and IIIb eliminate these separations by the use of p-nitrotoluene as a starting material. However, the oxidation methods available are difficult to control, and are accompanied by low reported yields.

The steps described in IIIc and IIId involve an expensive separation of mono- from di-chlorinated compounds by vacuum fractionation, since these compounds have corrosive properties and high boiling points.

The simultaneous oxidation and reduction outlined in IIIe and IIIf appears to have good possibilities, and possesses none of the disadvantages already mentioned in connection with other methods. In view of these considerations, further investigation has been concentrated on the development of this method.

p-Aminobenzaldehyde. The simultaneous oxidation and reduction of p-nitrotoluene to produce p-amino benzaldehyde by the use of alkaline polysulfides was discovered quite some years ago, and was patented by Geigy & Co. (German) patent 86874 (1895).[28]

Several variations of this preparation are described[1,10,17,21,23,27] The main difficulties met in these preparations were formation of thio- derivatives through use of excess sulfur; incomplete oxidation, from insufficient sulfur, resulting in by product p-toluidine; and self condensation to form a Schiff's base (dimer) or higher polymers, with resultant loss of yields. This latter reaction is accelerated by acids, especially traces of mineral acids.[21]

The sulfur requirement was thoroughly investigated by Beard and Hodgson,[1] who concluded that the sulfur must be present in such proportions as to form sodium tetrasulfide in the alkaline (sodium hydroxide) medium,

in order to achieve maximum conversion to the desired p-aminobenzaldehyde. They report yields up to 74.6%.

Huey and Rollschafer[17] have patented an acetylation procedure which immediately follows the synthesis of p-aminobenzaldehyde, in order to protect it from self condensation.

p-Acetamidocinnamic acid. It is interesting to note here that the Perkin condensation, using sodium acetate and acetic anhydride, which was used to convert benzaldehyde and nitrobenzaldehyde to the corresponding cinnamic acids, could not be utilized with p-amino- or p-acetamidbenzaldehydes.[18] Due to the influence of negative substituents such as NH_2 or CH_3CONH- in the p-position the Perkin condensation will not take place with these latter substituted benzaldehydes. It was therefore necessary to resort to a condensation with malonic acid in pyridine solution, in the presence of a secondary amine such as piperidine or dimethylamine[3,18,19,26] as described by Knoevenagel, Doebner, and Shoppee. The latter has reported 78% conversion by this method.

p-Acetamidocinnamic ester. The Fischer-Speier method of esterification seems quite reliable, and has been used with nitrocinnamic acids.[8,11] Amino-

substituted acids such as p-aminobenzoic acid have also been esterified commercially by this method. However, the investigation of this method, to complete the synthesis of p-acetamidocinnamic ester, was not undertaken in the present work.

EXPERIMENTAL

p-Amino- and p-Acetamidobenzaldehyde

1. Attempted preparation of sodium polysulfide (Huey and Rollschafer).[17] Following the method described in the patent literature, 55 gm of sulfur flowers were stirred into 90 gm of 30% sodium hydroxide solution at 80 - 90°C, resulting in incomplete solution. Two hundred fifty gm additional of water was added and the mixture was again stirred and heated. Some more sulfur appeared to dissolve, only to reprecipitate on standing. Since a homogeneous polysulfide mixture was not achieved, this method was discarded in favor of a more satisfactory one.

2. Preparation of p-acetamidobenzaldehyde. The method of Huey and Rollschafer[17] was followed, but with a different sodium polysulfide preparation. On the basis of 55 gm of sulfur required for the oxidation and reduction, preparation of sodium tetrasulfide was attempted.

Eighty-three gm sodium sulfide nonahydrate, 257 ml of water, and 44 gm of sulfur flowers were stirred together and heated. All but the minor portion of the sulfur dissolved; this slight excess was filtered off. The solution was stored one week, with only slight

additional precipitation of sulfur being noted.

This solution was added to a solution of 91 gm p-nitrotoluene in 300 ml of ethyl alcohol (SD 3A) at 78 - 80° C over a two hour period. The mixture was then refluxed for two hours additional, and alcohol was removed by distillation.

The resulting heavy oily layer was drawn off while hot, and heated with 78 ml of acetic anhydride. During the above separation, yellow crystals of unreacted p-nitro toluene formed in the aqueous layer. After the acetylated mixture stood for five days, a deposit of red crystals formed.

The crystalline mass was broken up and mixed with 251 ml of water and the mixture was adjusted to pH 6.5 - 6.8 with sodium hydroxide pellets. Sixty gm of sodium bisulfite (55 gm sodium metabisulfite) was added to the above mixture and stirred. A pasty solid formed, which dissolved on heating to 50° C, but re-formed when cooled to 25° C. After the liquor was removed by filtration, the cake was slurried several times with water. The combined filtrate and washes were made alkaline with sodium hydroxide pellets and p-acetamido benzaldehyde was precipitated. The solid was filtered, washed, and dried. M.P. 147 - 149° C

(p-acetamidobenzaldehyde). Barely enough yield was obtained to be able to determine its melting point.

The residue cake was heated with diluted hydrochloric acid, cooled, and filtered. The filtrate was neutralized with sodium carbonate, and the resulting precipitate, about 3 gm, was filtered, washed, and dried. M.P. 150° C (n-acetyl p-toluidine).

The solid residue cake was steam distilled and recrystallized from benzene. About 1 gm of large colorless crystals formed. M.P. 51° C (unreacted p-nitrotoluene).

3. Preparation of p-acetamidobenzaldehyde. Technical grade sodium polysulfide flake was obtained. Assuming this to be mainly sodium tetrasulfice, 75 gm should contain the required 55 gm of sulfur. Therefore, 75 gm of the flake sodium polysulfide were dissolved in 300 ml of water, and run into a mixture of 91 gm of p-nitrotoluene in 300 ml of ethanol, at 78 - 80° C. The mixture was then refluxed three hours at 83° C. The alcohol was distilled off and the residual oily layers separated while hot. During the separation, an upper aqueous phase, and two non aqueous phases resulted. The two non aqueous phases were acetylated separately, each with 78 ml of acetic

anhydride.

A small portion of the crimson lighter oil was dissolved in alcohol, but would not crystallize. However the oil gave a phenylhydrazone, M.P. 173° C from ethanol, indicating derivation from p-aminobenzaldehyde.

Both of the above acetylations were quite vigorous, and when complete, were cooled over the week end. Each was then poured into 250 ml of water and neutrallized to pH 6.8 with sodium carbonate. Fifty five gm of sodium metabisulfite was added to each portion and stirred. The resulting cakes were filtered, and the liquors precipitated with sodium hydroxide pellets. The filtered and washed precipitates were recrystallized from ethanol, M.P. 153° C. Both proved to be p-acetamidobenzaldehyde. The total yield was estimated to be about 3 gm.

The residue cakes (from bisulfite treatment) were recrystallized from ethanol. Both produced a yellow crystalline material, M.P. 145° C (N-acetyl-p-toluidine, by product). The total yield was estimated to be almost 10 gm.

Some of the p-acetamidobenzaldehyde was converted to the phenylhydrazone, M.P. 209° C, from ethanol. It was therefore proved that the products of both the

non-aqueous phases were identical, although one contained mostly product, and the other, mostly by-product.

4. Preparation of p-acetamidobenzaldehyde. After the method described in Organic Synthesis,[23] a rapid addition of the polysulfide reagent was tried. Eighty gm of flake sodium polysulfide (a slight excess) were dissolved in 300 ml of water, preheated to 70° C, and about half run at 70° C into a mixture of 91 gm of p-nitrotoluene in 300 ml of ethanol. At this point, a vigorous reaction started and addition was stopped momentarily. When boiling had stopped, addition was resumed at a rate so as to maintain refluxing at 84° C. When the addition was complete, external heat was applied, and the mixture was refluxed at 84° C for a total reaction time of two and one half hours.

The ethanol was then distilled off until the temperature reached 100° C. The oily layer was next separated, while hot, in a preheated separatory funnel and washed once with hot water. The separated oil was slowly poured into 78 ml of acetic anhydride and refluxed at 95° C for three hours. The acetylated mixture was poured into 250 ml of water and neutralized with sodium hydroxide pellets.

Fifty five gm of sodium metabisulfite was added

with good stirring. At this point, the mixture solidified into lumps which were very difficult to treat. Therefore, 500 ml of chloroform were added until all solids were in solution, either in the chloroform, or in the bisulfite-aqueous phase. After shaking well, the aqueous layer was drawn off and precipitated with sodium hydroxide pellets. The finely divided precipitate was slow in filtration, and was allowed to stand over the week end. The filtered and washed precipitate was dried at 110° C, yielding 12 gm of crude material (11% of theory). The theoretical yield of p-acetamidobenzaldehyde is 108.2 gm.

The chloroform layer was evaporated and dried at 110° C, yielding 43 gm of crude n-acetyl p-toluidine, (43.4%). If no oxidation took place, this reaction should produce 99 gm of this compound.

The foregoing yields account for only 54.4% of the total material involved. Therefore, the methods of recovery are at fault and improvement is needed.

5. Preparation of p-aminobenzaldehyde. Since most of the difficulty in the foregoing experiments arose from the formation of insoluble solids, as a result of the acetylations, a similar preparation was made, omitting the acetylation step.

The polysulfide solution, as before, was added over a one hour period, followed by three hours of refluxing. After distilling off the alcohol, the mixture was extracted while warm (50 - 55° C), with two portions of chloroform (500 ml and 100 ml).

The chloroform extracts were then shaken with 55 gm $Na_2S_2O_5$ in 250 ml of water. The resulting bisulfite addition compound solidified, and after drawing off the chloroform, was extracted repeatedly with warm water. The filtered aqueous extracts were precipitated with sodium hydroxide pellets. Upon filtering, washing, and drying, 26.7 gm (33.2%) of crude p-aminobenzaldehyde were obtained.

The dried solid bisulfite residue was heated with 1000 ml of alcohol, filtered, and diluted with three volumes of water containing a little sodium bisulfite. The slight resulting turbidity was removed by filtration with Hiflow filter aid, and the solution made alkaline with sodium hydroxide pellets. The recovered precipitate, upon drying, yielded an additional 3.5 gm p-aminobenzaldehyde, (4.4%); total yield, 37.6%.

Upon evaporation, the chloroform layer yielded 6.3 gm of impure p-toluidine, as an oil. No phenylhydrazone could be obtained from this oil, indicating

the absence of any aldehyde. The total recovery was then 8.9% by-product and 46.5% product.

In addition to difficults all ready mentioned, traces of chloroform were carried into the sodium hydroxide precipitation. This produced a foul, pungent odor due to formation of traces of an isocyanide.

Acetylation of p-aminobenzaldehyde. Since the previous acetylation was thought to aid self condensation, 21.2 gm of dried p-aminobenzaldehyde were suspended in 100 ml of pyridine, and warmed to 50° C. Twenty five ml of acetic anhydride was added over a 10 minute period, with stirring. The mixture was then heated to 60° C, and allowed to cool. The mixture was chilled with ice and filtered. The resulting cake was dried, slurried in sodium carbonate solution at pH 7.5. This was filtered, washed, and dried, yielding 11.5 gm (39.8%) of p-acetomidobenzaldehyde.

6. Attempted preparation of p-acetamidobenzaldehyde. Ninety-one gm of p-nitrotoluene was treated as before, and after distilling off the alcohol, the resulting oil was separated while hot. In an attempt to find a method of acetylation which would reduce the tendency of the p-aminobenzaldehyde to polymerize, a low-temperature acetylation described by Fieser[29] was

tried. The oil was run into a mixture of 1500 ml of water and 50 ml concentrated hydrochloric acid. This was warmed to 50° C, and 70 ml of acetic anhydride were added, followed immediately by a solution of 90 gm of sodium acetate crystals in 300 ml of water. The mixture was cooled in an ice bath, the solids filtered off, washed, and dried. The greater portion of this material was a dark red gum, insoluble in alcohol. The dark red color, and lack of solubility indicated that the material was largely a condensation polymer of no further value.

7. Attempted preparation of p-aminobenzaldehyde. In order to determine the effect of inverted addition of the reactants, 91 gm of p-nitrotoluene in alcohol solution at 60° C was added over a 1-3/4 hour period to the solution of flake polysulfide at 70 - 85° C with efficient mechanical agitation. After the first half hour, the alcohol was distilled off as the addition continued. When all the alcohol was distilled, the mixture was steam distilled to a clear distillate.

The residue in the flask, upon separation, weighed only 5.2 gm, assumed to be product. On this basis, the 72 gm of steam distilled solids should have contained 47.2 gm of p-toluidine by product, and 24.8 gm of p-nitrotoluene, unreacted. It was obvious that this

method was not at all satisfactory.

8. Preparation of p-aminobenzaldehyde. This preparation was based on the method described by Beard and Hodgson.[1] Their work pointed out the necessity of ethyl alcohol and sodium polysulfide as tetrasulfide in this reaction, and eliminated the slow addition, used in other methods.

Fifty gm p-nitrotoluene, 30 gm $Na_2S \cdot 9 \sim H_2O$, 12.5 gm sulfur flowers, 22.5 gm sodium hydroxide, 600 ml of water, and 300 ml of alcohol were stirred together with good mechanical agitation, and heated to reflux, 84° C.

After refluxing for 90 minutes, a clear homogenous mixture resulted, from which the alcohol was then distilled. p-Toluidine was then removed by steam distillation, and clear distillate was obtained after about 800 ml had passed over. A very small amount of oil (about 1 ml) separated from the distillate, on standing.

Most of the oily layer was separated from the reaction mixture while hot, and after chilling, the remaining oil was removed. Thirty gm of $Na_2S_2O_5$ in 250 ml of water was added to the oil, and stirred. To aid mixing, ether was added, shaken, and drawn off. The ether portion yielded 4 gm (9.6%) of p-aminobenzaldehyde.

The aqueous portion was filtered and adjusted to pH 8 with sodium carbonate. The precipitate was filtered, washed with ice water, and dried. Yield, 10.5 gm (23.7%) of p-aminobenzaldehyde. Total yield, 33.3%.

9. Preparation of p-Aminobenzaldehyde. In view of the small portion of by product in the steam distillate, in the previous experiment, a great deal more product p-aminobenzaldehyde was produced in the reaction than was recovered. In order to increase this recovery, and at the same time eliminate the emulsions encountered when shaking out with ether, (the oil solidifies on cooling) an exhaustive liquid extraction with a higher boiling ether was proposed.

The reaction was run as in the previous experiment, and after the steam distillation, the mixture was sent out for extraction with isopropyl ether, in a liquid-liquid extraction apparatus. After some hours of still extraction, the extract was returned and evaporated to dryness. Yield, 15 gm of light yellow orange p-amino benzaldehyde were obtained, (34%). It was later learned that this extraction was not carried to exhaustion, as is done in Soxhlet principle extractions.

Because of the time elapsed between reaction and

extraction, a lot of the oil had solidified upon cooling, and may have been harder to extract than a liquid would have been.

10. Preparation of p-aminobenzaldehyde. In spite of emulsion possibilities, and lack of special equipment, a hot extraction of the reaction mixture was attempted.

The reaction was run as before, but before the steam stripped mixture had cooled, below 50° C, it was shaken out several times with isopropyl ether. Upon further cooling, oil became very viscous, and aggravated emulsion formation in subsequent extractions.

The filtered extracts were evaporated and dried in vacuo, yielding 20.1 gm p-aminobenzaldehyde, (45.7%).

The steam distillate was extracted with ether, and gave 4 gm of orange colored oil, which gave no phenyl hydrazone derivative. It therefore could have contained only p-toluidine and unchanged p-nitrotoluene.

p-Amino- and p-Acetamidocinnamic Acids

The next series of experiments were made to check the malonic acid condensation described by Shoppee,[26] and to investigate the necessity of acetylating p-amino benzaldehyde before the condensation was carried out.

This acetylation is covered by Huey's patent,[17] and has not been very successful in those methods tried, due to the tendency of the amino group to condense with the aldehyde group in preference to becoming acetylated. Therefore, if p-aminobenzaldehyde will successfully condense with malonic acid to form the cinnamic acid, this p-aminocinnamic acid could then be acetylated with no further denger of self condensation.

11. Preparation of p-acetamidocinnamic acid. Eleven and one half gm of p-acetamidobenzaldehyde, from experiment 5, and 7.48 gm of malonic acid were heated on a boiling water bath in 17.5 ml of pyridine and 0.7 ml of piperidine.

The pasty mass soon went into solution, and a steady evolution of CO_2 began. After two hours, the evolution of gas ceased, and the mixture was poured into 200 ml of ice water containing 17.5 ml of glacial acetic acid.

At this point, some precipitate formed, but most of the product separated as a viscous oil which slowly solidified upon cooling. The aqueous solution was filtered off, and the crude product recrystallized from boiling ethanol. Yield, 1.7 gm (11.8%), M.P. 258° C. Pure p-acetamidocinnamic acid melts at 261° C.

12. Attempted preparation of p-aminocinnamic acid. Twenty and one-tenth gm of p-aminobenzaldehyde, from experiment 10, and 17.35 gm of malonic acid were heated with 41.4 ml of pyridine and 1.65 ml of piperdine as in the previous experiment. Upon pouring this mixture into 700 ml of ice water and 40.5 ml of acetic acid, a small amount of precipitate and a large amount of red oil were obtained.

The precipitate was separated, dissolved in sodium hydroxide solution, and reprecipitated with acetic acid. Upon drying, this tan precipitate melted at 166° C. The melting point of pure p-aminocinnamic acid is 176° C. There was not enough of this material to weigh.

The oil resisted solution with solvents, acetic acid, or sodium hydroxide, but dissolved in concentrated hydrochloric acid. After heating with charcoal, and filtering, the solution was made alkaline to pH 10 with sodium hydroxide. The lemon yellow precipitate was filtered, washed, and dried. This material melted above 280° C, and from its reactions, was assumed to be the hydrochloride of p-aminobenzaldehyde, which should melt some 200° C above the melting point of the amine.[20]

It was apparent that since the p-aminobenzaldehyde was exposed to the action of the malonic acid in this

experiment, before the addition of the pyridine and piperidine catalyst, it must have formed a polymer, which later broke down to monomer when treated with concentrated hydrochloric acid. Therefore this experiment was repeated, taking care to add the malonic acid to the mixture last.

13. Preparation of p-aminocinnamic acid. Fourteen and one half gm of p-aminobenzaldehyde, from experiment 9, were suspended in a mixture of 29.8 ml of pyridine and 1.19 ml of piperdine over a boiling water bath. Twelve and one half gm of malonic acid were then added, and the mixture heated for two hours.

The mixture was then poured into 500 ml of ice water containing 30 ml of concentrated hydrochloric acid. A large volume of orange precipitate was filtered, washed, and dried. Crude yield, 13.4 gm (68.4%).

A portion of the crude material was recrystallized from boiling water, M.P. 168° C. p-Aminocinnamic acid melts at 175° C. A second portion was converted to the sodium salt, using sodium carbonate solution. A yellow precipitate formed upon neutralization with dilute hydrochloric acid, but as pH was lowered to decompose excess carbonate, it changed to a light orange color. This probably indicated the formation

of the hydrochloride of p-amino cinnamic acid, first precipitated. This theory was borne out when the dried material was very difficult to melt (greater than 280° C). This hydrochloride is estimated to melt at 375° C, no data available.

The hydrochloric acid was used in the initial precipitation, instead of acetic acid as in previous experiments, in order to aid solution of any unreacted p-aminobenzaldehyde which might tend toward oil formation with the p-aminocinnamic acid precipitate.

EXPERIMENTAL SUMMARY

Oxidation and Reduction of p-Nitrotoluene

In order to better correlate the various reaction and recovery conditions tried in these experimental runs, the yields together with the more pertinent factors are tabulated below.

Table I

Yields and Conditions of Treatment

Run	Yield	Remarks
?	--	Reaction incomplete, no excess alkali.
3	--	Flake polysulfide, products identified.
4	11.0%	Flake polysulfide, 43.4% by product.
5	37.6%	Hot chloroform extraction, Bisulfate isolation, no acetylation.
6	nil	Yield lost in acetylation.
7	nil	Reverse addition, little reaction.
8	3[illegible].3%	Sodium tetrasulfide, steam distillation, chilled separation, bisulfite isolation.
9	34.0%	Same, except cold continuous extraction.
10	45.7%	Same, except hot hand extraction.

Discussion. The results tabulated above serve to point out the contribution of certain factors toward increasing yields in the simultaneous oxidation and reduction of p-nitrotoluene with sodium polysulfides.

First, it is noted that sodium tetrasulfide provides more product with a minimum of by product than those polysulfides of other compositions. This also confirms the findings of Beard and Hodgson.[1]

The main reason for the low yield in run 7 was attributed to low alcohol concentration by virtue of the reverse addition, and rapid removal of the solvent. Beard et al found this to be true, and also proved the advantage of ethanol over other alcohols. The presence of some methanol (Special Denatured alcohol #3A was used in all these experiments), about 10%, may account for the fact that the yields reported with ethanol[1] were not here realized. However, this last possibility has not been confirmed.

The acetylation methods tried seemed to contribute little toward preventing self condensation, or toward facilitating recovery.

The use of steam distillation as a means of by product removal seems unnecessary, when sodium tetra sulfide is used, since the small percentage of p-toluidine by-product may be eliminated by other methods.

The use of a hot solvent as a means of removing p-aminobenzaldehyde, while liquid, from the reaction

mixture has given good recovery in runs 5 and 10. The use of chloroform, however, is not recommended in combination with amines and hot alkali, because of the formation of poisonous and undesireable isocyanides. Isopropyl ether has proven satisfactory, and benzene might also be used.

The bisulfite addition compound of p-aminobenzaldehyde has formed a pasty mass on every occasion and presents a lot of handling difficulties. This step might well be eliminated and isolation done by other means, possibly in the next step of the synthesis.

The liquid-liquid extraction used in (9) affords the ideal method of recovery from the aqueous alkaline reaction mixture. This special apparatus recycles a continuous flow of redistilled solvent through the aqueous liquid batch to be extracted. With suitable modification to keep the extraction chamber heated to just below the solvent boiling point, the rate of solution would be greatly increased. In the case at hand, this is still more important since the material to be extracted becomes viscous, then solid, at lower temperatures. The lack of shaking in this extractor also minimizes the formation of emulsions with the alkaline solution.

The yields obtained by Beard et al[1] were isolated by condensation with phenylhydrazone, a method which is of no value, if p-aminobenzaldehyde is desired as product.

Condensations with Malonic Acid.

The only method tried in these condensations was that described by Shoppee[26] in his preparation of p-dimethylaminocinnamic acid. He reported a 78% yield in a similar condensation using p-acetamidobenzaldehyde, but gave no further details of the method.

In the first condensation, p-acetamidobenzaldehyde was used, but gave only 11.8% yield, due to enough impurities present to prevent proper crystallization of the product.

The second run (12), was made using p-aminobenzaldehyde, but since the reactants were not combined in any special order, a great deal of self condensation took place, and the run had to be repeated.

Taking care to add the malonic acid last, and using hydrochloric acid in the precipitation, produced a yield of 68.4% of p-aminocinnamic acid in run 13. This latter change has the advantage over acetic acid as a precipitant, since impurities and by products such as

p-toluidine and unreacted p-aminobenzaldehyde tend to remain in solution. This precipitation might well also serve as the main separation of by-product carryover from the oxidation-reduction reaction.

CONCLUSIONS AND RECOMMENDATIONS

Preparation of p-Aminobenzaldehyde

Mechanism of the reaction. As pointed out by Beard and Hodgson,[1] the final products of the treatment of p-nitrotoluene with sodium polysulfide are determined by the composition of the polysulfide reagent.

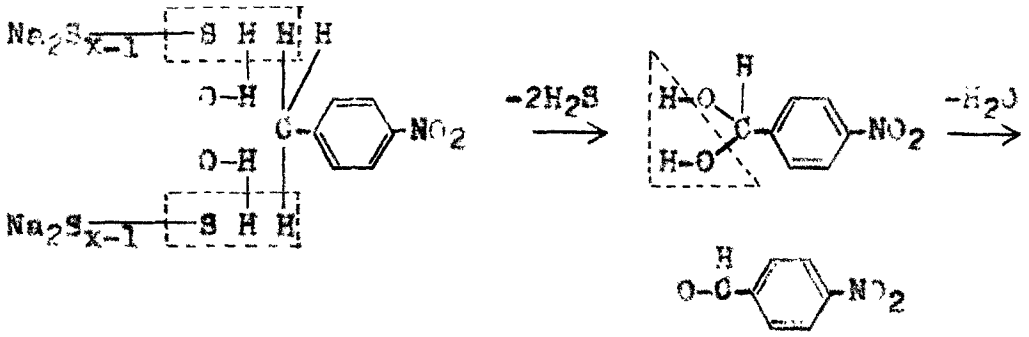
In order to promote oxidation of the methyl group, there must be sufficient loosely bound sulfur present to act as an oxidizing agent. This has been found to be most efficient when sodium tetrasulfide or an equivalent mixture is used.

In an aqueous, alcoholic, alkaline medium, this sulfur attacks the methyl group of p-nitrotoluene (IX), and converts it to an aldehyde group, liberating hydrogen sulfide. This hydrogen sulfide reacts with the alkali present, to form sodium hydrosulfide. As the result of sulfur loss, the tetra sulfide becomes monosulfide, and then the monosulfide and hydrosulfide attack the nitro group, reducing it to amine. When only monosulfide is present, reduction but no oxidation takes place.

The overall reaction may be represented by the equation:

$$2\ Na_2S_4 + 6\ (CH_3\text{-}Ph\text{-}NO_2) + 4\ NaOH \longrightarrow$$
$$6(CHO\text{-}Ph\text{-}NH_2) + 2\ NaHS + 2\ Na_2S_2O_3 + H_2O$$

where 0.33 mol of sodium tetrasulfide and 0.67 mol of sodium hydroxide are required for each mol of p-nitro toluene. The oxidation of the methyl group takes place according to schematic representation given by Beard and Hodgson:[1]



Specific reaction conditions. The best conditions for proper direction of reaction progress are given in the following example. (One gm mol of p-nitrotoluene requires one-third gm mol of sodium tetrasulfide.) To 600 ml of water are added in order, 22.5 gm of sodium hydroxide pellets, 30 gm of sodium sulfide nonohydrate, 12 gm of sulfur flowers, 50 gm of p-nitro toluene, and 300 ml of ethanol. If the latter must be denatured, Special Denatured formula 28 (benzene) is recommended, to avoid possible lowered yields from denaturants such as methanol.

Good mechanical agitation is recommended from the

start of the addition, throughout the reaction time. When the reactants are all added, a reflux condenser is attached, and heating commenced. The reaction takes place over a 90 minute period at the reflux temperature, 84 - 85° C.

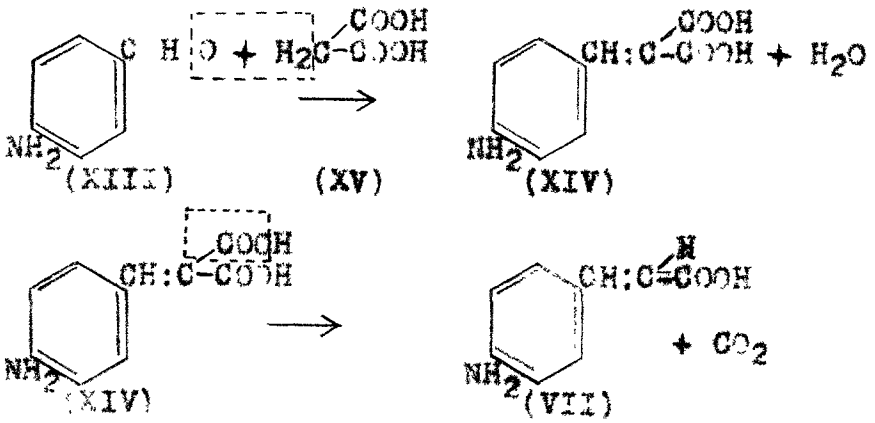
Separation and recovery of product. When the above reaction conditions are followed, only about 10% of by-products are formed. These have been successfully removed by steam distillation, but the high temperature involved may have a detrimental effect, such as accelerating polymerization of the desired p-aminobenzaldehyde. Therefore, a hot solvent extraction is recommended for the removal of all organic compound from the reaction mixture, and by-product separation may be done later. Isopropyl ether has been quite satisfactory for this purpose, and benzene might also be used. The latter had the advantage of drying the extracted material as the solvent is distilled off. Chlorinated solvents are not recommended.

p-Aminobenzaldehyde crystallized quite well from both isopropyl ether, and benzene, and may be recrystallized at this point if desired, rather than being completely recovered by evaporation. It is concluded that in view of the following step in the synthesis, the removal of by products may be easier

after the malonic acid condensation, rather than by use of sodium bisulfite at this point.

Preparation of p-Aminocinnamic acid.

Mechanism of malonic acid condensation. When an aromatic aldehyde (XIII) is heated in a basic medium such as pyridine, with traces of a secondary base, piperidine, as a catalyst, the beta carbon of malonic acid (XV) condenses with the aldehyde group, eliminating a molecule of water. This condensation produces an unsaturated beta diacid (XVI). The diacid is then partially decarboxylated by loss of one molecule of carbon dioxide, and the unsaturated monoacid (VII) is produced.



In the case at hand, it has been noted that one additional precaution is necessary, with p-amino benzaldehyde. In order to prevent self condensation by direct action of a strong (malonic) acid, it was found

necessary to first combine the amino-aldehyde with the catalyst and basic medium, and add the condensing agent, malonic acid, last.

Specific reaction conditions. The recommended procedure for the malonic acid condensation is set forth in the following example. To a solution of 1.19 ml of piperidine in 29.8 ml of pyridine, is added 14.5 gm of p-aminobenzaldehyde, and the mixture is heated to 100° C. An equimolar quantity, 12.5 gm of malonic acid is then added, and the mixture stirred under reflux at this temperature for two hours. The evolution of carbon dioxide should have ceased, otherwise heating is continued until this occurs.

Separation and recovery of product. The reaction mixture, above, is poured with good stirring, into 500 ml of ice water containing about 30 ml of concentrated hydrochloric acid. At this point, any p-toluidine by product from the previous reaction, and any unreacted p-aminobenzaldehyde present should dissolve as their hydrochlorides, leaving the p-aminocinnamic acid to be precipitated out.

If this precipitation is to be combined with the aforementioned separation, it is recommended that the precipitated acid be redissolved in sodium hydroxide,

filtered to remove additional amino-aldehyde, and reprecipitated with hydrochloric acid. This last neutralization should be carried only to pH about 6.5 in order to avoid hydrochloride formation at low pH.

Completion of the Synthesis

The following recommendations are not supported by experimental findings, since the preparations lie beyond the scope of this paper.

Preparation of p-acetamidocinnamic acid. This preparation possesses no apparent difficulty in the form of side reactions, now that no aldehyde group is present. Therefore it appears that a straight forward acetylation with acetic anhydride could be easily done.

Preparation of p-acetamidocinnamic esters. The only method found in the literature[6] for such an esterification was accomplished by the Fischer-Speier method, using a solution of the substituted cinnamic acid in the proper alcohol, catalyzed by a stream of dry hydrogen chloride.

SUMMARY

A number of variations of the simultaneous oxidation and reduction of p-nitrotoluene were found in the literature. The variations of Beard and Hodgson,[1] Canonigne, et al,[10] Huey and Rollschafer,[17] and Lieberman and Conner[21] were tried experimentally. The reaction conditions of Beard and Hodgson were found to produce the best yields.

In view of a more convenient separation of by products after conversion of p-aminobenzaldehyde to p-aminocinnamic acid, it was found that steam stripping of by products, immediately following the formation of p-aminobenzaldehyde, could be omitted.

The inconvenient isolation of p-aminobenzaldehyde through its sodium bisulfite addition compound was also found to be unnecessary for the reasons just given.

A hot solvent extraction of the reaction mixture was found to be the most efficient method for recovery of p-aminobenzaldehyde, regardless of reaction conditions.

Through the use of a solvent extraction, the crude p-aminobenzaldehyde was obtained in a form suitable for use in the malonic acid condensation. These p-amino-

benzaldehyde crystals were sufficiently stable over short periods that the need for acetylation at this point was found to be unnecessary.

The malonic acid condensation method described by Shopree[26] was found to be quite satisfactory, provided that the malonic acid was added to the reaction mixture last.

The precipitation of p-aminocinnamic acid, and dissolution of entrained p-toluidine, was found to be successful when hydrochloric acid was substituted for the acetic acid used by Shopree.[26]

LITERATURE CITED AND BIBLIOGRAPHY

1. Beard and Hodgson, J. Chem. Soc. (London) 1944, pp. 4-5.
2. Bernthsen, A., and Sudborough, J. J., Organic Chemistry, p. 511, Blackie & Sons Ltd., 1941 Ed.
3. Ibid., p. 512.
4. Ibid., p. 724.
5. Buckles, R. E., Chem. Abstr., 44, p. 5163e.
6. Corvin, J. H., Chem. Abstr., 44, p. 8377d.
7. Dippy, J. F. J., and Evans, R. H., Chem. Abstr., 44, p. 9378e.
8. Davey, W., and Gwilt, J. R., Chem. Abstr., 44, p. 9936a.
9. Miklukhin, G.P., Chem. Abstr., 45, p. 545e.
10. Chem. Abstr., 46, p. 934c. (See reference 23).
11. Derbentseva, N. H., Chem. Abstr., 46, p. 10229i.
12. Cohen, J. B., Practical Organic Chemistry, pp. 248, 441, Macmillan & Co., Ltd., 3rd Ed. reprinted 1937.
13. Gatterman, L.; revised by Wieland, H., Laboratory Methods of Organic Chemistry, p. 232, (translation of 24th German Ed.) Macmillan & Co. Ltd., 1943.
14. Heilbron, I., Dictionary of Organic Compounds. Oxford University Press, 1953.

15. Horning, J. Org. Chem., 11, p. 95, 1946.

16. Houben and Weyl, Die Methoden der Organischen Chemie, II, pp. 7-9, Georg Thieme, Liepzig.

17. Huey, W. G., and Rollschafer, B. W., U. S. Patent 2,608,582, 1952.

18. Johnson, J. R. (Roger Adams, editor), Organic Reactions, I, pp. 218-219, John Wiley & Sons, 1942.

19. Ibid., pp. 234, 263.

20. Kamm, O., Qualitative Organic Analysis, 2nd Ed., John Wiley & Sons, 1932.

21. Lieberman, S. V., and Conner, R., (Blatt' Organic Synthesis, Coll. Vol. II, p. 441, John Wiley & Sons.

22. Mann, F. G., and Saunders, B. D., Practical Organic Chemistry, p. 161, Longmans, Green & Co. Ltd., 2nd Ed., 1942.

23. Campaigne, E., Budde, W. M., and Schaefer, G. F., (R. S. Schreiber, editor), Organic Synthesis, 31, pp. 6-8, John Wiley & Sons, 1951.

24. Reid, E. E., College Organic Chemistry, p. 574, (4th printing, 1934), D. Van Nostrand & Co., 1929.

25. Ibid., p. 575.

26. Shoppee, J. Chem. Soc. (London), 1930, p. 968.

27. Ullman, Enzyklopadier Technichen Chemie, II, pp. 211-212, Urban & Schwarzburg, Berlin, 1928.

28. Beilstein's Handbuch der Organischen Chemie, XIV, p. 24, Julius Springer, Berlin, 1931.

29. Fieser, L. F., and Fieser, M., Organic Chemistry, pp. 637, 672, 2nd Ed., D. C. Heath & Co., 1950.